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SEARCH REQUEST FORM

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Requester's Full Name: Natalie Davis Examiner #: 78462 Date: 6-15-01
Art Unit: 1642 Phone Number 308-6410 Serial Number: 09/724406
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Title of Invention: _____ CRF'd

Inventors (please provide full names): _____

Earliest Priority Filing Date: 11-28-2000

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Please search claims 1-9, 11, & 13-19 & Seq ID NO: 2

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1, 6, 8, 12, 13, 15, 19

20, 22, 24, 28, 30, 32

26

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PTO-1590 (1-2000)

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Set     Items   Description
S1     109709   HODGKIN?
S2       4895   CD30 OR CD()30
S3        610   (ANTIBOD? OR IMMUNOGLOBULIN? ?)(5N) S2
S4        365   S3 AND S1
S5        161   S4 AND (TREAT? OR ADMINISTER? OR DELIVER? OR PREVENT? OR T-
           HERAP?)
S6          7   S5 AND (FUSION? OR CHIMER?)
S7        154   S5 NOT S6
S8          4   RD S6 (unique items)
S9         25   S7 AND CULTURE? ?
S10       129   S7 NOT S9
S11        19   RD S9 (unique items)
S12        27   S10 AND (CONJUGAT? OR LINK?)
S13       102   S10 NOT S12
S14        18   RD S12 (unique items)
S15        41   S8 OR S11 OR S14
?t 15/7/all

 15/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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11272446   21248724   PMID: 11351308
 Isolation of new anti-CD30 scFvs from DNA-immunized mice by phage display
and biologic activity of recombinant immunotoxins produced by  fusion with
truncated pseudomonas exotoxin.
  Rozemuller H; Chowdhury PS; Pastan I; Kreitman RJ
  Laboratory  of  Molecular  Biology,  National  Cancer Institute, National
Institutes of Health, Bethesda, MD, USA.
  International journal of cancer.  Journal international du cancer (United
States)  Jun  15  2001,  92  (6)  p861-70,  ISSN 0020-7136  Journal Code:
GQU
  Languages: ENGLISH
  Document type: Journal Article
  Record type: In Process
  To target CD30 on Hodgkin 's disease and anaplastic large-cell lymphoma,
anti- CD30  single-chain antibodies  were obtained by DNA immunization of
mice  with  the  complete  human CD30 cDNA. Spleens were isolated from mice
with  high  anti-CD30  titer, and the RNA was used for the production of an
scFv-displaying phage library. Specific phages were enriched by 3 rounds of
panning  on  soluble  CD30  or CD30(+) K562 cells. Recombinant immunotoxins
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(rITs) were made from 3 ELISA-positive scFv phages by fusion to a 38 kDa truncated mutant of Pseudomonas exotoxin (PE38) with or without a KDEL mutant sequence at the C terminus. In vitro cytotoxicity of purified anti-CD30 rITs was measured on CD30-transfected A431 cells. IC(50) values ranged from 3 to 7 ng/ml (50-110 pM) for PE38 rITs and 0.1 ng/ml (2 pM) for the PE38-KDEL IT on A431-CD30 cells. The parental A431 cells were resistant, indicating that the cytotoxicity was specific and CD30-mediated. rITs were tested for anti-tumor activity in a nude mouse model. A431-CD30 cells were injected s.c. on day 0; then, mice bearing measurable tumors were treated beginning on day 4 with 3 alternate daily doses i.v. Anti-tumor activity was dose-dependent and not found when irrelevant ITs were administered or when CD30(-) tumors were treated . Our data show that DNA immunization and antibody phage display may be useful in producing new rITs against hematologic malignancies. Published 2001 Wiley-Liss, Inc.
Record Date Created: 20010514

15/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11259891 21214453 PMID: 11313991
CD30-mediated cell cycle arrest associated with induced expression of p21(CIP1/WAF1) in the anaplastic large cell lymphoma cell line Karpas 299.
Hubinger G; Muller E; Scheffrahn I; Schneider C; Hildt E; Singer BB; Sigg I; Graf J; Bergmann L
Department of Internal Medicine III, University of Ulm, Robert-Koch-Str. 8, D-89081 Ulm, Germany.
Oncogene (England) Feb 1 2001, 20 (5) p590-8, ISSN 0950-9232
Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
One of the major characteristics of anaplastic large cell lymphomas (ALCL) is the expression of the Ki-1/CD30 antigen. While the receptor mediates NF-kappaB-activation in Hodgkin 's lymphomas, some data suggest the CD30-mediated apoptosis of other CD30-expressing cells. We were able to demonstrate that activation of CD30 leads to different effects regarding cell proliferation of the ALCL-derived cell lines Karpas 299 and JB6. Western and Northern blotting analysis revealed that CD30-induced growth inhibition of Karpas 299 cells correlated with a strong upregulation of the cell cycle inhibitor p21(CIP1/WAF1). We found a non activating point mutation at codon 273 in exon 8 of the p53 gene in Karpas 299 cells which indicates an p53-independent mechanism for induced p21 expression. Abundant p21 protein expression resulted in hypophosphorylation of the retinoblastoma protein (Rb) and inhibition of the proliferating cell nuclear antigen (PCNA). CD30-stimulated cells showed no indications of apoptotic cell death, like genomic DNA fragmentation or cleavage of the caspase-3 target protein poly (ADP-ribose) polymerase (PARP). Our results indicate that CD30 is able to mediate an p21-associated cell cycle arrest in ALCL with possible implications for prognosis and clinical treatment .
Record Date Created: 20010423

15/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10859897 20485774 PMID: 11029515
Recombinant immunotoxins for the treatment of Hodgkin's disease (Review).
Matthey B; Engert A; Barth S
Department I of Internal Medicine, University of Cologne, Germany.
International journal of molecular medicine (GREECE) Nov 2000, 6 (5) p509-14, ISSN 1107-3756 Journal Code: C8H
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
In recent years, substantial experience has been accumulated with tumor-specific immunotherapeutics which seem to be effective against minimal residual disease. The coupling of toxins to monoclonal antibodies has indicated promising results in early clinical trials. Recombinant DNA technology makes it possible to genetically fuse coding regions of V genes or cytokines to modified toxin domains. These recombinant immunotoxins can easily be manipulated to increase the cytotoxic potency or affinity. Binding single-chain variable fragments (scFv) expressed as chimeric fusion proteins on the surface of filamentous bacteriophages were selected on Hodgkin -derived cell lines. This technique was also used to create a new humanized anti-CD30 scFv which exhibits similar binding to the CD30 antigen when compared to its murine predecessor. ScFvs were then inserted into a new bacterial expression vector and thus fused to a deletion mutant of Pseudomonas exotoxin. Anti-CD25(scFv)-ETA' and anti-CD30(scFv)-ETA' were isolated from E. coli periplasm and purified by metal chelate affinity and size exclusion chromatography. All immunotoxins produced showed specific cytotoxicity against Hodgkin lymphoma cell lines as documented by competitive assays. In addition, these constructs were highly efficient in the treatment of disseminated human Hodgkin 's disease in SCID mice. These in vivo data indicate a possible clinical impact for patients with relapsed CD25- and/or CD30-positive lymphoma. (19 Refs.)
Record Date Created: 20001027

15/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10707096 20405078 PMID: 10950145
Immune recruitment by bispecific antibodies for the treatment of Hodgkin disease.
da Costa L; Renner C; Hartmann F; Pfreundschuh M
Department of Internal Medicine I, Saarland University Medical School, Homburg/Saar, Germany.
Cancer chemotherapy and pharmacology (GERMANY) 2000, 46 Suppl pS33-6, ISSN 0344-5704 Journal Code: C9S
Languages: ENGLISH
Document type: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Journal Article
Record type: Completed
For the treatment of Hodgkin lymphoma, bispecific monoclonal antibodies (bi-mAbs) were established which recognize the Hodgkin -associated CD30 antigen with one arm and the CD3 or CD28 antigen on T lymphocytes or the CD16 antigen on natural killer (NK) cells with the second arm. The NK cell-activating alpha-CD16/CD30 antibody was able to

125

retarget human NK cells toward CD30- target cells and induce their lysis. Sixty percent of Hodgkin tumor-bearing severe combined immunodeficient mice responded to a combined treatment with bi-mAb and human NK cells, leading to a final cure rate of 20%. T cell-activating bi-mAbs were more effective, resulting in the cure of all mice treated . The in vivo administration of both alpha-CD3/CD30 and alpha-CD28/CD30 antibodies resulted in the specific activation of resting human T cells infiltrating the CD30+ Hodgkin tumors. Tumor-infiltrating lymphocytes in the group of mice treated with both T cell-activating bi-mAbs expressed high levels of cytokines and cytotoxic molecules such as perforin and the cytotoxic serine esterases granzyme A and B. More importantly, activated T cells did not home to CD30 tissue and did not enter the circulation. Encouraged by these preclinical data, 15 patients with treatment -refractory Hodgkin lymphoma were included in a phase I/II dose-escalation study and treated four times every 3 or 4 days with increasing doses of the alpha-CD16/CD30 bi-mAb ranging from 1 mg/m2 to 128 mg/m2. No dose-limiting toxicity occurred even at the highest doses. Of these 15 patients, one had a complete response, one a partial response, three a mixed response, two stable disease, and eight patients had progressive disease. Treatment with immunological effector cell-recruiting bi-mAbs is a promising new approach to the treatment of Hodgkin disease refractory to standard therapy .

Record Date Created: 20000906

15/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10672918 20304495 PMID: 10845927

Ki-4(scFv)-ETA', a new recombinant anti-CD30 immunotoxin with highly specific cytotoxic activity against disseminated Hodgkin tumors in SCID mice.

Barth S; Huhn M; Matthey B; Tawadros S; Schnell R; Schinkothe T; Diehl V; Engert A

Medizinische Klinik I der Universitat zu Koeln, Cologne, Germany. stefan.barth@uni-koeln.de

Blood (UNITED STATES) Jun 15 2000, 95 (12) p3909-14, ISSN 0006-4971 Journal Code: A8G

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

1/2,4

The human lymphocyte activation marker CD30 is highly overexpressed on Hodgkin /Reed-Sternberg cells and represents an ideal target for selective immunotherapy. We used the murine anti-CD30 hybridoma Ki-4 to construct a new recombinant immunotoxin (rIT) for possible clinical use in patients with CD30(+) lymphoma. Hybridoma V genes were polymerase chain reaction-amplified, assembled, cloned, and expressed as a mini-library for display on filamentous phage. Functional Ki-4 scFv obtained by selection of binding phage on the CD30-expressing Hodgkin lymphoma cell line L540cy was inserted into the bacterial expression vector pBM1.1 and fused to a deletion mutant of Pseudomonas exotoxin A (ETA'). Periplasmically expressed Ki-4(scFv)-ETA' demonstrated specific activity against a variety of CD30(+) lymphoma cells as assessed by different in vitro assays. To evaluate in vivo antitumor activity, severe combined immunodeficient mice challenged with human lymphoma cell lines were treated with the immunotoxin. The blood distribution time t(1/2)alpha of Ki-4(scFv)-ETA' was 19 minutes, and

its serum elimination time t(1/2)alpha was 193 minutes. A single intravenous injection of 40 microg rIT 1 day after tumor inoculation rendered 90% of the mice tumor free, extending the mean survival time to more than 200 days compared with 38.1 days in the phosphate-buffered saline control group (P <.001). This new rIT is a promising candidate for further clinical evaluation in patients with Hodgkin lymphoma or other CD30(+) malignancies. (Blood. 2000;95:3909-3914)
Record Date Created: 20000810

15/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10672549 20356551 PMID: 10901379
Human anti- CD30 recombinant antibodies by guided phage antibody selection using cell panning.
Klimka A; Matthey B; Roovers RC; Barth S; Arends JW; Engert A; Hoogenboom HR
Department of Internal Medicine I, University Hospital Cologne, Germany.
British journal of cancer (SCOTLAND) Jul 2000, 83 (2) p252-60, ISSN 0007-0920 Journal Code: AV4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In various clinical studies, Hodgkin 's patients have been treated with anti-CD30 immunotherapeutic agents and have shown promising responses. One of the problems that appeared from these studies is the development of an immune response against the nonhuman therapeutics , which limits repeated administration and reduces efficacy. We have set out to make a recombinant, human anti- CD30 single-chain variable fragment (scFv) antibody , which may serve as a targeting moiety with reduced immunogenicity and more rapid tumour penetration in similar clinical applications. Rather than selecting a naive phage antibody library on recombinant CD30 antigen, we used guided selection of a murine antibody in combination with panning on the CD30-positive cell line L540. The murine monoclonal antibody Ki-4 was chosen as starting antibody, because it inhibits the shedding of the extracellular part of the CD30 antigen. This makes the antibody better suited for CD30 -targeting than most other anti- CD30 antibodies . We have previously isolated the murine Ki-4 scFv by selecting a mini-library of hybridoma-derived phage scFv-antibodies via panning on L540 cells. Here, we report that phage display technology was successfully used to obtain a human Ki-4 scFv version by guided selection. The murine variable heavy (VH) and light (VL) chain genes of the Ki-4 scFv were sequentially replaced by human V gene repertoires, while retaining only the major determinant for epitope-specificity: the heavy-chain complementarity determining region 3 (CDR3) of murine Ki-4. After two rounds of chain shuffling and selection by panning on L540 cells, a fully human anti-CD30 scFv was selected. It competes with the parental monoclonal antibody Ki-4 for binding to CD30 , inhibits the shedding of the extracellular part of the CD30 receptor from L540 cells and is thus a promising candidate for the generation of anti-CD30 immunotherapeutics.
Record Date Created: 20000808

15/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10349186 99445364 PMID: 10515858
A bispecific diabody that mediates natural killer cell cytotoxicity against xenotransplantated human Hodgkin's tumors.
Arndt MA; Krauss J; Kipriyanov SM; Pfreundschuh M; Little M
Recombinant Antibody Research Group (D0500), German Cancer Research Center (DKFZ), Heidelberg, Germany.
Blood (UNITED STATES) Oct 15 1999, 94 (8) p2562-8, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
CD16/ CD30 bispecific monoclonal antibodies can induce remissions of Hodgkin 's disease refractory to chemo- and radiotherapy. However, the development of human antimouse immunoglobulin antibodies and allergic reactions precludes repeated applications of the antibody. Moreover, problems of producing and purifying sufficient amounts of material limit the clinical practicability of this novel treatment approach. To overcome these obstacles, we have constructed a bispecific antibody in a diabody form that only employs the variable domains of the CD16/CD30 hybrid hybridoma. The diabody compared favorably with the parent CD16/CD30 bispecific antibody in its ability to activate and target natural killer cells in vitro. Its administration to mice bearing xenografted Hodgkin 's lymphoma resulted in a marked regression of tumor growth, thus proving for the first time the capability of a diabody for immune recruitment in vivo. The CD16/CD30 diabody is a novel reagent that should considerably facilitate the immunotherapy of patients with refractory Hodgkin 's lymphoma.
Record Date Created: 19991122

15/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09888288 98403728 PMID: 9734659
Targeting of saporin to Hodgkin's lymphoma cells by anti- CD30 and anti-CD25 bispecific antibodies.
Sforzini S; de Totero D; Gaggero A; Ippoliti R; Glennie MJ; Canevari S; Stein H; Ferrini S
Istituto Nazionale per la Ricerca sul Cancro, Centro di Biotecnologie Avanzate, Genova, Italy.
British journal of haematology (ENGLAND) Sep 1998, 102 (4) p1061-8, ISSN 0007-1048 Journal Code: AXC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1,2,4
CD25 and CD30 represent suitable target molecules for bispecific antibody (bimAb)-driven toxin delivery to lymphoid tumour cells. We describe two new anti-CD30/anti-saporin bimAbs (termed CD30 x sap1 and CD30 x sap2), produced by hybrid hybridomas, which react against non-cross-reactive epitopes of the saporin molecule, and compared their effect with a bimAb reacting with saporin and with CD25 (CD25 x sap1). In a protein synthesis inhibition assay these bimAbs were able to enhance saporin toxicity (IC50 = 8.5 x 10(-9) M in the absence of mAbs) with a similar activity: in the presence of 10(-9) M CD30 x sap1 bimAb the IC50 was 2.75 x 10(-11) M,

whereas with CD30 x sap2 bimAb the IC50 was 6.5 x 10(-11) M and CD25 x sap1 bimAb displayed an IC50 of 3 x 10(-11) M (as saporin). The combined use of the two anti-CD30 bimAbs further increased cytotoxicity by 100-fold, resulting in an IC50 of 1.9 x 10(-13) M. A slightly less efficient improvement was obtained by combining the CD25 x sap1 bimAb with the CD30 x sap2 bimAb directed against a different toxin epitope (saporin IC50 to 7 x 10(-13) M). In contrast, no synergistic effect was observed using the combination of the anti-CD25 bimAb with the anti-CD30 bimAb reacting with the same epitope of saporin (IC50 = 4.5 x 10(-11) M). Analysis of FITC-saporin binding to L540 cells by flow cytometry demonstrated that the appropriate combinations of the two anti-CD30/anti-saporin bimAbs or of the anti-CD30/anti-saporin and anti-CD25/anti-saporin bimAbs had a cooperative effect on the binding of the ribosome-inactivating protein (RIP) to the cells, when compared with single bimAbs.

Record Date Created: 19981016

15/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09193585 97060442 PMID: 8903477

Induction of apoptosis by ribosome-inactivating proteins and related immunotoxins.

Bolognesi A; Tazzari PL; Olivieri F; Polito L; Falini B; Stirpe F
Dipartimento di Patologia Sperimentale, Universita Bologna, Italy.

International journal of cancer. Journal international du cancer (UNITED STATES) Nov 4 1996, 68 (3) p349-55, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Immunotoxins have been prepared with 3 ribosome-inactivating proteins (RIPs), namely, momordin, pokeweed anti-viral protein from seeds (PAP-S) and saporin, linked to the Ber-H2 monoclonal antibody directed against the CD30 antigen of human lymphocytes. Either the RIPs or the immunotoxins induced apoptosis in the CD30+ L540 cell line, as shown by the morphological aspects of the cells, by the DNA fragmentation visible at the electrophoresis, and by the formation of DNA breaks evidenced by 2 cytofluorometric techniques (propidium-iodide staining and fluoresceine-isothiocyanate conjugate dUTP incorporation). The AC50 (concentration causing apoptosis in 50% of the cells) is in the range 10(-8) to 10(-7) M in the case of RIPs, and 10(-11) to 10(-10) M in the case of the immunotoxins.

Record Date Created: 19961223

15/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08903781 96083728 PMID: 7591296

A zinc metalloproteinase is responsible for the release of CD30 on human tumor cell lines.

Hansen HP; Kisseleva T; Kobarg J; Horn-Lohrens O; Havsteen B; Lemke H
Department of Biochemistry, University of Kiel, Germany.

International journal of cancer. Journal international du cancer (UNITED

STATES) Nov 27 1995, 63 (5) p750-6, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The activation marker CD30 is expressed on the cell surface of the malignant cells in Hodgkin 's disease and a few non-Hodgkin lymphomas. We have analyzed the regulation of membrane-bound CD30 and found that the binding of a variety of anti-CD30 antibodies induced down-regulation of CD30 on cell lines. In addition, such down-modulation was also observed after treatment of the cell surface proteins with the sulfhydryl reagent iodoacetamide or after stimulation of the second messenger pathway with phorbol ester or calcium ionophore. This modulation was abolished at 4 degrees C and strongly inhibited by chelators like EDTA or 1,10-phenanthroline, whereas EGTA, a selective inhibitor of Ca(2+)-dependent proteinases and other inhibitors of serine, thiol and acid proteinases, showed no effect. The down-modulation was strengthened by Zn2+ or Cd2+, but not by other divalent cations such as Fe2+, Mn2+, Mg2+, Ca2+ or Co2+, thus indicating the involvement of a zinc metalloproteinase in CD30 modulation which can be activated by protein kinase C and by alkylation of sulfhydryl groups. Pulse-chase experiments, analysis of the CD30 glycosylation and specific measurement of the 90-kDa soluble form of CD30 (sCD30) with a sandwich radioimmunoassay revealed that CD30 down-modulation results from enhanced release of 90-kDa sCD30 by the site-specific cleavage of CD30 accomplished by a zinc metalloproteinase. This release occurs at the cell membrane without prior endocytosis.

Record Date Created: 19951228

15/7/11 (Item 11 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08869101 96197365 PMID: 8625370

Interleukin-12 increases bispecific-antibody-mediated natural killer cell cytotoxicity against human tumors.

Sahin U; Kraft-Bauer S; Ohnesorge S; Pfreundschuh M; Renner C

Med. Klinik I, University of Saarland Medical School, Homburg/Saar, Germany.

Cancer immunology, immunotherapy (GERMANY) Jan 1996, 42 (1) p9-14, ISSN 0340-7004 Journal Code: CN3

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The combination of CD16/ CD30 bispecific monoclonal antibodies (bi-mAb) and unstimulated human resting natural killer (NK) cells can cure about 50% of mice with severe combined immunodeficiency (SCID) bearing subcutaneously growing established Hodgkin 's lymphoma. As interleukin-2 (IL-2) and IL-12 have been shown to increase NK cell activity, we tested the capacity of these cytokines to increase bi-mAb-mediated NK cell cytotoxicity against two types of human tumors (Hodgkin 's disease and colorectal carcinoma). Unstimulated NK cells needed a three- to five-times higher antibody concentration than cytokine-stimulated NK cells to exert similar levels of bi-mAb-mediated cytotoxicity. The augmented tumor cell lysis was achieved with IL-12 at considerably lower concentrations than with IL-2 and was associated with a significantly increased bi-mAb-mediated intracellular Ca2+ mobilization. The efficiency of IL-12 in this setting

together with its low toxicity make it the ideal candidate for a combination therapy with NK-cell-activating bi-mAb in human tumors that are resistant to standard treatment .
Record Date Created: 19960626

15/7/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08868025 96194481 PMID: 8616080
Anti-CD30 (BER=H2) immunotoxins containing the type-1 ribosome-inactivating proteins momordin and PAP-S (pokeweed antiviral protein from seeds) display powerful antitumour activity against CD30+ tumour cells in vitro and in SCID mice.
Terenzi A; Bolognesi A; Pasqualucci L; Flenghi L; Pileri S; Stein H; Kadin M; Bigerna B; Polito L; Tazzari PL; Martelli MF; Stirpe F; Falini B
Institute of Haematology, University of Perugia, Italy.
British journal of haematology (ENGLAND) Mar 1996, 92 (4) p872-9, ISSN 0007-1048 Journal Code: AXC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The anti-CD30 immunotoxin (IT) Ber-H2/saporin is effective in patients with refractory Hodgkin 's disease. However, responses are short and partial, one of the main reasons being the inability to repeat IT doses because of formation of human antibodies against the murine antibody and/or the toxin. To overcome this problem, we constructed two new anti-CD30 ITs by covalently linking the mouse monoclonal antibody Ber-H2 to the type 1 ribosome-inactivating proteins (RIPs) momordin (MOM) and pokeweed antiviral protein from seeds (PAP-S), which do not cross-react with each other or with saporin. Both ITs inhibited protein synthesis by Hodgkin 's disease and anaplastic large-cell lymphoma (ALCL)-derived CD30+ target cell lines with a very high efficiency (IC50 ranging from < 5 x 10(-13) M to 2.75 x 10(-11) M, as RIP). In a SCID mouse model of xenografted CD30+ human ALCL, a 3d treatment with non-toxin doses of Ber-H2/MOM (50%LD50), started 24 h after transplantation, prevented tumour development in about 40% of the animals and significantly delayed tumour growth rate in the others. Main toxicity signs in mice and rabbits were dose-related increase of serum transaminases (AST and ALT) and creatine phosphokinase (CPK). LD50 (as RIP) in Swiss mice was 7 mg/kg for Ber-H2/MOM and 0.45 mg/kg for Ber-H2/PAP-S. Sequential administration of two anti-CD30 ITs (Ber-H2/MOM and Ber-H2/saporin) was well tolerated and did not result in formation of antibodies cross-reacting and with the two plant toxins. The results presented in this paper suggest that in the future, sequential administration of anti- CD30 humanized antibodies linked to antigenically distinct type 1 RIPs (saporin, MOM, PAP-S) should be feasible.
Record Date Created: 19960612

15/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08808056 96129478 PMID: 8581380
Targeting of type 1 ribosome-inactivating proteins to CD30+ or CD25+

hematologic neoplasias by bispecific antibodies.

Sforzini S; Bolognesi A; Meazza R; Marciano S; Tazzari PL; Stein H; Stirpe F; Ferrini S

Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.

Journal of hematotherapy (UNITED STATES) Oct 1995, 4 (5) p429-32, ISSN 1061-6128 Journal Code: B3T

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

In this study, we compared the ability of different bispecific monoclonal antibodies (BsmAb) and immunotoxins to deliver the type 1 ribosome-inactivating proteins (RIP) saporin and gelonin through the CD25 or CD30 target molecules to Hodgkin 's lymphoma cells. An anti-CD25/antisaporin and an anti-CD30/antisaporin BsmAb enhanced the toxicity of the relevant RIP against the CD25+CD30+ L540 Hodgkin 's lymphoma cell line, although targeting by anti-CD30 BsmAb appeared eight times more efficient. Two anti-CD30/antigelonin BsmAb, reacting with different epitopes of the gelonin molecule, were able to enhance gelonin toxicity against L540 cells and had a synergistic effect when used in combination. Among CD25-CD30+ Hodgkin 's lymphoma lines, which were resistant to targeting by anti-CD25/saporin BsmAb, one (L428) was sensitive to both gelonin and saporin delivered by anti-CD30 BsmAb. Another CD25-CD30+ cell line (COLE) was completely resistant to the toxic effect of gelonin targeted by the two synergistic BsmAb, as well as to an anti-CD30/gelonin immunotoxin. However, these cells were partially sensitive to saporin delivered by an anti-CD30/anti-saporin BsmAb, and they were efficiently killed by an anti-CD30/saporin immunotoxin. These results indicate that heterogeneity in the sensitivity to certain RIP, such as gelonin, exists among tumor cells of the same histotype.

Record Date Created: 19960320

15/7/14 (Item 14 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08800896 96043734 PMID: 7591211

Development of new ricin A-chain immunotoxins with potent anti-tumor effects against human Hodgkin cells in vitro and disseminated Hodgkin tumors in SCID mice using high-affinity monoclonal antibodies directed against the CD30 antigen.

Schnell R; Linnartz C; Katouzi AA; Schon G; Bohlen H; Horn-Lohrens O; Parwaresch RM; Lange H; Diehl V; Lemke H; et al

Medizinische Universitatsklinik I, Cologne, Germany.

International journal of cancer. Journal international du cancer (UNITED STATES) Oct 9 1995, 63 (2) p238-44, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The lymphocyte activation marker CD30 has been shown to be an excellent target for the immunotherapy of human Hodgkin 's lymphoma. In order to develop new potent immunotoxins (ITs) against CD30, we chemically linked 6 recently described monoclonal antibodies (MAbs) via SMPT to deglycosylated ricin A-chain (dgA). Cross-blocking experiments demonstrated that these MAbs, termed Ki-2 to Ki-7, recognize 3 different clusters on the CD30 antigen: Ki-2, Ki-4, Ki-5 and Ki-7 recognize cluster A; Ki-6

recognizes cluster B; Ki-3 binds to cluster C. Staining of 29 sections of normal human organs revealed no major cross-reactivity of any MAbs tested. Binding to the CD30 antigen on L540Cy Hodgkin cells was assessed by flow cytometry, and demonstrated high affinities for Ki-2, Ki-3 and Ki-4. The concentration giving 50% of the mean fluorescence intensity (MFI50) was 0.58 micrograms/ml to 0.78 micrograms/l. MAbs Ki-5, Ki-6, and Ki-7 bound much more weakly. The staining intensity of the MAbs correlated with the cytotoxicity of the corresponding ITs. Ki-2.dgA, ki-3.dgA and Ki-4.dgA inhibited the protein synthesis of L540Cy cells by 50% at concentrations (IC50) of 3.5 x 10(-10)M to 4.0 x 10(-11)M. The most effective IT, Ki-4dgA, is 5-fold more potent than previously reported CD30 ricin A-chain ITs. Ki-4.dgA was subsequently used for the treatment of disseminated human Hodgkin 's lymphoma in a SCID mouse model. The mean survival time (MST) of lymphoma-bearing SCID mice was extended from 42 days in untreated controls to more than 132 days when Ki-4.dgA was applied one day after tumor challenge. Ki-4.dgA is a new potent IT suitable for further evaluation against Hodgkin 's lymphoma in man.

Record Date Created: 19951204

15/7/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08774953 95374906 PMID: 7646996

Differential sensitivity of CD30+ neoplastic cells to gelonin delivered by anti- CD30/anti-gelonin bispecific antibodies.

Sforzini S; Bolognesi A; Meazza R; Marciano S; Casalini P; Durkop H; Tazzari PL; Stein H; Stirpe F; Ferrini S

Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.

British journal of haematology (ENGLAND) Jul 1995, 90 (3) p572-7, ISSN 0007-1048 Journal Code: AXC

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Lymphocyte activation antigens, such as CD30 , represent suitable target molecules for antibody -driven drug delivery in haemopoietic malignancies. A ribosome-inactivating protein (RIP) type 1 of potential interest for mAb targeting is gelonin, which displays a lower toxicity, as compared to other RIPs. In this study, two anti- CD30 /antigelonin bispecific monoclonal antibodies (bimAbs), secreted by hybrid hybridomas, were used to deliver this RIP to CD30+ tumour cells. The two bimAbs, termed D4 and A18, were produced using the same anti-CD30 mAb and two anti-gelonin mAbs, directed to unrelated epitopes of the gelonin molecule. These bimAbs enhanced gelonin toxicity (IC50 5 x 10(-8) M, in the absence of mAbs) against the CD30+ L540 Hodgkin 's lymphoma cell line in a protein synthesis inhibition assay. Thus, in the presence of 10(-9) M D4 bimAb, protein synthesis was inhibited with an IC50 of 5 x 10(-10) M as gelonin, whereas with A18 bimAb the IC50 was 8 x 10(-11) M. More interestingly, the combined use of the two bimAbs had a synergistic effect, since the IC50 of gelonin reached 6 x 10(-12) M. Among CD30 tumour cell lines, the Hodgkin 's lymphoma L428 was also sensitive to gelonin delivered by bimAbs (IC50 6 x 10(-11) M), whereas the COLE Hodgkin 's cell line and the T-ALL Jurkat were completely resistant to the toxic effect of gelonin and bimAbs. COLE and Jurkat cells were also resistant to a gelonin/anti-CD30 conventional immunotoxin, whereas they were sensitive to a saporin/anti-CD30 immunotoxin. This suggests that the resistance to gelonin is not related to

a lack of internalization through the CD30 molecule but is associated with some property of the RIP.
Record Date Created: 19950925

15/7/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08764152 95130290 PMID: 7530238
Shedding of the soluble form of CD30 from the Hodgkin-analogous cell line L540 is strongly inhibited by a new CD30-specific antibody (Ki-4).
Horn-Lohrens O; Tiemann M; Lange H; Kobarg J; Hafner M; Hansen H; Sterry W; Parwaresch RM; Lemke H
Biochemical Clinic, Medical Faculty of the Christian-Albrechts University, Kiel, Germany.
International journal of cancer. Journal international du cancer (UNITED STATES) Feb 8 1995, 60 (4) p539-44, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The CD30-activation marker was detected as the Hodgkin -associated Ki-I antigen and is regarded as a target for the treatment of Hodgkin patients with immunotoxins. The CD30 is released from tumor cells and this soluble CD30 (sCD30) is an indicator of the disease activity. Since the shedding of sCD30 may be influenced by antibodies , we produced 6 new CD30 -specific antibodies (Ki-2 to Ki-7) for the purpose of finding antibodies that might inhibit the formation of sCD30. Ki-2 to Ki-7 and the other anti-CD30 antibodies Ki-I, Ber-H2, HeFi-I, M44, M67, HRS-I, HRS-4 and C10 were employed for epitope mapping. The binding of a particular radio-labeled anti- CD30 antibody to Hodgkin 's-disease-derived L540 cells was completed by addition of the various non-labeled anti-CD30 antibodies . Three non-overlapping regions, expressing different antigen-specific determinants, could be defined on the extracellular part of the CD30 molecule. Cluster A of determinants was recognized by Ki-2, Ki-4, Ki-6 and Ki-7, Ber-H2, HRS-I and HRS-4, while cluster B was detected by Ki-I, Ki-5 and M67. Cluster C, which probably contains the binding site for the CD30 ligand, was defined by Ki-3, M44, HeFi-I and C10. Co-culture experiments of L540 cells with the various antibodies followed by the isolation of sCD30 from culture supernatant fluids revealed that the release of sCD30 was most strongly increased by Ki-I and weakly enhanced by Ki-2, Ki-3, Ki-5 and HeFi-I, whereas it was almost completely inhibited by Ki-4 and to a slightly lesser extent by Ber-H2.
Record Date Created: 19950222

15/7/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08642832 96062190 PMID: 7585597
In vivo antitumor effects of unconjugated CD30 monoclonal antibodies on human anaplastic large-cell lymphoma xenografts.
Tian ZG; Longo DL; Funakoshi S; Asai O; Ferris DK; Widmer M; Murphy WJ
Laboratory of Leukocyte Biology, National Cancer Institute-Frederick Cancer Research and Development Center, Maryland 21702, USA.

Cancer research (UNITED STATES) Nov 15 1995, 55 (22) p5335-41, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

CD30 is a M(r) 120,000 surface antigen identified originally by the Ki-1 monoclonal antibody (moAb) against primary and cultured Reed-Sternberg cells present in Hodgkin 's disease and anaplastic large-cell lymphomas (ALCLs). Examination of two ALCL cell lines (Karpas 299 and Michel) demonstrated cell surface expression of CD30. Incubation of these lymphomas with two anti-CD30 moAbs that recognize the ligand-binding site (M44 or HeFi-1) resulted in significant growth inhibition in vitro, with significant decreases in cell viability. Another anti-CD30 moAb, Ber-H2, which recognizes a determinant not involved in ligand binding, had no effect on ALCL growth in vitro. When these human ALCL lines were transferred i.v. into mice with severe combined immune deficiency, the mice developed extensive metastasis in the s.c., brain, or eye tissues. The treatment of mice with either M44 or HeFi-1 anti-CD30 moAbs resulted in significant increases in survival, with some mice remaining disease free for more than 100 days. Thus, anti-CD30 treatment is efficacious for CD30+ ALCL cell lines in vivo, and unconjugated anti-CD30 moAbs may be of potential clinical use.

Record Date Created: 19951215

15/7/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08252863 95012112 PMID: 7927236

In vivo and in vitro uptake of an anti-CD30/saporin immunotoxin by rat liver parenchymal and nonparenchymal cells.

Battelli MG; Buonamici L; Bolognesi A; Stirpe F
Dipartimento di Patologia Sperimentale, Universita di Bologna, Italy.

Hepatology (UNITED STATES) Oct 1994, 20 (4 Pt 1) p940-7, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

A Ber-H2/saporin immunotoxin, consisting of the single-chain ribosome-inactivating protein saporin-S6 and the anti-CD30 monoclonal antibody Ber-H2, gave encouraging results in the treatment of refractory Hodgkin 's disease but caused a transient hepatotoxicity. The accumulation of Ber-H2/saporin conjugate and of its components by rat liver parenchymal and nonparenchymal cells was studied. The in vivo concentration of intravenously injected Ber-H2/saporin, saporin or Ber-H2 in nonparenchymal cells was 4-, 25- and 11-fold higher, respectively, than that in parenchymal cells. Adherent in vitro cultured nonparenchymal cells, mostly Kupffer cells, accumulated the proteins approximately 10 times more than parenchymal cells; traces of free saporin were taken up by both types of cells. In vitro protein synthesis by both cell types was inhibited by 50% at nanomolar concentrations of saporin. Nonparenchymal cells were sensitive to Ber-H2/saporin at picomolar concentrations, whereas parenchymal cells were unaffected by the immunotoxin up to 100 pmol/L. The results of the uptake of, and the sensitivity to, the immunotoxin suggest that the sensitivity of liver cells is proportional to the uptake and that the in vivo damage to parenchymal cells is at least in part mediated by the

toxicity to nonparenchymal liver cells.
Record Date Created: 19941028

15/7/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08050237 94064175 PMID: 8244580
A CD16/ CD30 bispecific monoclonal antibody induces lysis of Hodgkin 's cells by unstimulated natural killer cells in vitro and in vivo.
Hombach A; Jung W; Pohl C; Renner C; Sahin U; Schmits R; Wolf J; Kapp U; Diehl V; Pfreundschuh M
Medizinische Klinik, Universitat des Saarlandes, Homburg/Saar, Germany.
International journal of cancer. Journal international du cancer (UNITED STATES) Nov 11 1993, 55 (5) p830-6, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In order to target NK cells against the Hodgkin 's-derived cell line L540, we developed bispecific monoclonal antibodies (Bi-MAbs) by somatic hybridization of the 2 mouse hybridoma cell line HRS-3 and A9 which produce monoclonal antibodies (MAbs) with reactivity against the Hodgkin and Reed-Sternberg cell-associated CD30 antigen and the CD16 antigen (Fc gamma III receptor), respectively. The CD16 MAb-producing cell line A9 was selected as a partner for HRS-3 because of its efficiency in inducing lysis of the A9 hybridoma cells by resting NK cells. The hybrid hybridoma cell line HRS-3/A9 produced the supernatant with the strongest bispecific reactivity and was repeatedly subcloned and used for ascites production. Crude supernatant and purified HRS-3/A9 Bi-MAb triggered specific lysis of the CD30+ Hodgkin 's-derived cell line L540, but not of the CD30- cell line HPB-ALL by unstimulated peripheral-blood lymphocytes and NK-cell-enriched populations. Moreover, treatment of SCID mice bearing heterotransplanted human Hodgkin 's tumors with HRS-3/A9 and human peripheral blood lymphocytes induced specific complete tumor regression in 10/10 animals. We thus report successful tumor treatment in an in vivo model using NK-cell-associated Bi-MAbs and show that the Bi-MAb HRS-3/A9 is an efficient promoter of the anti-tumor effects of NK cells in vitro and in vivo.
Record Date Created: 19931223

15/7/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07820113 93081391 PMID: 1333274
Experimental therapy in Hodgkin's disease.
Engert A; Pohl C; Diehl V
Medizinische Universitatsklinik I, Universitat zu Koln, Germany.
Annals of oncology (NETHERLANDS) Sep 1992, 3 Suppl 4 p97-100, ISSN 0923-7534 Journal Code: AYF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Hodgkin /Reed-Sternberg (H-RS) cells express lymphoid activation markers

like CD25 and CD30 which are present only on a small minority of normal cells. Currently, most experimental approaches in Hodgkin 's lymphoma are aimed at targeting H-RS cells via monoclonal antibodies against CD25 and CD30 : immunotoxins constructed by linking the antibody moiety chemically to deglycosylated ricin A-chain destroy up to 60% of small H-RS tumors in mice. The most potent immunotoxin is currently being scaled up for clinical trials. Other experimental strategies use bispecific constructs that, after binding to the cell surface of H-RS cells, convert prodrugs into their toxic counterparts, or employ monoclonal antibodies for active immunotherapy.
Record Date Created: 19930106

15/7/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07818190 92261143 PMID: 1349939
Response of refractory Hodgkin 's disease to monoclonal anti-CD30 immunotoxin.
Falini B; Bolognesi A; Flenghi L; Tazzari PL; Broe MK; Stein H; Durkop H; Aversa F; Corneli P; Pizzolo G; et al
Institute of Haematology, University of Perugia, Italy.
Lancet (ENGLAND) May 16 1992, 339 (8803) p1195-6, ISSN 0140-6736 Journal Code: L0S
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In Hodgkin 's disease, Hodgkin and Reed-Sternberg cells consistently express the antigen CD30. We investigated the possible therapeutic role of an immunotoxin prepared by covalent linking of an anti- CD30 monoclonal antibody (Ber-H2) to saporin (SO6), a type-1 ribosome-inactivating protein. The immunotoxin (0.8 mg/kg in one or two doses) was given to four patients with advanced refractory Hodgkin 's disease. In three, there was rapid and substantial reduction in tumour mass (50% to greater than 75%). Clinical responses were transient (6-10 weeks). In-vivo binding of the immunotoxin to tumour cells was shown by immunohistology in two patients. Antibodies to both parts of the immunotoxin developed in all patients.
Record Date Created: 19920618

15/7/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07347219 90243371 PMID: 2159438
Detection of a soluble form of the CD30 antigen in sera of patients with lymphoma, adult T-cell leukemia and infectious mononucleosis.
Pfreundschuh M; Pohl C; Berenbeck C; Schroeder J; Jung W; Schmits R; Tschiersch A; Diehl V; Gause A
Laboratory of Tumor Biology, University of Cologne, FRG.
International journal of cancer. Journal international du cancer (UNITED STATES) May 15 1990, 45 (5) p869-74, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article

Record type: Completed

Using a sandwich enzyme-linked immunosorbent assay (ELISA) we were able to detect a soluble form of the CD30 antigen (CD30s) in the supernatant of cell lines expressing membrane-bound CD30 and in T and B cells after transformation with human T-cell leukemia virus (HTLV-I) and Epstein-Barr-Virus (EBV). While CD30s was not found in 250 healthy controls, it was detected in the sera of patients with Hodgkin 's disease (23/100), anaplastic large-cell (6/9), angioimmunoblastic (2/2) and one unclassified high-grade non-Hodgkin 's lymphoma (NHL), as well as in 18/20 patients with acute adult T-cell leukemia (ATL, HTLV-I-positive). It was absent in a large number of patients with other high-grade NHL, all low-grade NHLs, acute or chronic leukemias and solid tumors. The only non-malignant disease with detectable levels of CD30s was infectious mononucleosis (9/10). The membrane-bound form of CD30 has a molecular weight of 120 kDa. Western blot analysis revealed that CD30s in the serum of patients has a molecular weight of 88 kDa, identical to the antigen released by cell lines in vitro. CD30s disappeared in all originally positive cases after successful treatment and reappeared in relapsing patients. Thus, CD30s may be useful as a specific marker for disease activity of certain types of lymphoma and ATL.

Record Date Created: 19900608

15/7/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06955419 90242258 PMID: 1692251

Antitumor effects of ricin A chain immunotoxins prepared from intact antibodies and Fab' fragments on solid human Hodgkin's disease tumors in mice.

Engert A; Martin G; Pfreundschuh M; Amlot P; Hsu SM; Diehl V; Thorpe P

Drug Targeting Laboratory, Imperial Cancer Research Fund, London, United Kingdom.

Cancer research (UNITED STATES) May 15 1990, 50 (10) p2929-35, ISSN 0008-5472 Journal Code: CNF

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Three monoclonal antibodies which strongly bind to Hodgkin and Reed-Sternberg cells and two corresponding Fab' fragments were linked to deglycosylated ricin A chain (dg A) to evaluate their potential as immunotoxins for the treatment of Hodgkin 's disease. Two of the antibodies, Ber-H2 and HRS-3, were shown to bind to the same epitope on the CD30 antigen, whereas the third antibody , IRac, bound to a different antigen. None of the antibodies significantly cross-reacted with normal human tissues as judged by indirect immunofluorescence and immunoperoxidase analyses on frozen sections from 28 normal tissues. All three antibodies formed potent and specific immunotoxins. They inhibited protein synthesis of the L540 Hodgkin 's disease cell line in vitro by 50% at concentrations of 1 x 10(-11) M for IRac.dgA, 9 x 10(-11) M for HRS-3.dgA, and 2 x 10(-10) M for Ber-H2.dgA. HRS-3 Fab' and IRac Fab' immunotoxins were 7.8- and 60-fold less cytotoxic, respectively, than their intact counterparts in vitro. In vivo, a single i.v. injection of a dose of Ber-H2.dgA, HRS-3.dgA, or IRac.dgA corresponding to 40% of the LD50 induced lasting complete remissions in 38, 44, and 50%, respectively, of mice with solid s.c. L540 tumors of 60 to 80 mm3 size (0.5-cm diameter). At equivalent dosage (40% of

the LD50), the HRS-3 Fab'.dgA and the IRac Fab'.dgA both induced lasting complete remissions in 25% of the mice, although the HRS-3 Fab'.dgA was significantly superior to IRac Fab'.dgA at retarding tumor growth in the remaining animals. The effectiveness of the immunotoxins depended on the size of the tumor at the time of injection, since IRac.dgA treatment induced complete remissions in 100% of mice with small tumors (10 to 20 mm3, approximately 0.3 cm in diameter) but only 13% of mice with larger tumors of 400 to 600 mm3 (approximately 1 cm in diameter). Tumors which regrew after IRac.dgA treatment mainly consisted of antigen-deficient mutants having reduced sensitivity to IRac.dgA but normal sensitivity to HRS-3.dgA. It is concluded that HRS-3.dgA, HRS-3 Fab'.dgA, and IRac.dgA are candidates for the treatment of Hodgkin 's disease in humans.
Record Date Created: 19900612

15/7/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06950826 90075158 PMID: 2152774
Evaluation of ricin A chain-containing immunotoxins directed against the CD30 antigen as potential reagents for the treatment of Hodgkin's disease.
Engert A; Burrows F; Jung W; Tazzari PL; Stein H; Pfreundschuh M; Diehl V ; Thorpe P
Drug Targeting Laboratory, Imperial Cancer Research Fund, London, United Kingdom.
Cancer research (UNITED STATES) Jan 1 1990, 50 (1) p84-8, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
See US 5,165,925
Five monoclonal CD30 antibodies and two Fab' fragments were linked to deglycosylated ricin A chain (dgA), and their potential as immunotoxins for the treatment of Hodgkin 's disease was evaluated. Cross-blocking experiments demonstrated that HRS-1, HRS-3, HRS-4, and Ber-H2 recognize the same epitope on the CD30 antigen and that Ki-1 binds to a different epitope. Scatchard analyses showed that HRS-3, HRS-4, and Ber-H2 bound strongly to L540 Hodgkin cells (Kd 15, 7, and 14 nM, respectively), whereas HRS-1 and Ki-1 bound more weakly (Kd 160 and 380 nM, respectively). The different affinities of the antibodies correlated closely with their cytotoxic potency as immunotoxins. HRS-3.dgA, HRS-4.dgA, and Ber-H2.dgA inhibited the protein synthesis of L540 cells by 50% at concentrations of 0.9-2.0 x 10(-10) M, whereas HRS-1.dgA and Ki-1.dgA were about 100 times less potent with 50% inhibitory concentrations of 0.8-1.0 x 10(-8) M. The most effective immunotoxins, HRS-3.dgA and HRS-4.dgA, were only 15 times less toxic than ricin itself. HRS-3 Fab'.dgA and HRS-4 Fab'.dgA were 7.8 and 3 times less potent than their IgG.dgA counterparts with 50% inhibitory concentrations of 7 x 10(-10) and 3 x 10(-10) M, respectively. Staining of human tissues revealed an unexpected cross-reactivity of HRS-4 with pancreatic cells of malignant and nonmalignant origin. HRS-1, HRS-3, Ber-H2, and Ki-1 showed very little cross-reactivity with any normal human tissues. It is concluded that HRS-3.dgA and HRS-3 Fab'.dgA are the immunotoxins of choice for in vivo therapy .
Record Date Created: 19900125

15/7/25 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12647882 BIOSIS NO.: 200000401384
Anti- CD30 antibodies preventing proteolytic cleavage and release of membrane-bound CD30 antigen.
AUTHOR: Lemke Hilmar(a); Hansen Hinrich-Peter
AUTHOR ADDRESS: (a)Achterwehr**Germany
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1232 (1):pNo pagination Mar. 7, 2000
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: An antibody which binds to the CD30 antigen and a) inhibits the release of sCD30 from Hodgkin 's disease cells, and b) does not bind to B cell non-Hodgkin 's lymphomas or plasma cells. An example of such antibodies are the antibodies secreted from hybridoma cell line DSM ACC 2204. The antibodies may be used for diagnosis, or conjugated to a toxin to produce an immunotoxin.

15/7/26 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12260331 BIOSIS NO.: 200000013833
Characterization of a chimeric T-cell receptor with specificity for the Hodgkin's lymphoma-associated CD30 antigen.
AUTHOR: Hombach Andreas; Heuser Claudia; Sircar Ranjan; Tillmann Thorsten; Diehl Volker; Pohl Christoph; Abken Hinrich(a)
AUTHOR ADDRESS: (a)Klinik I fuer Innere Medizin, Labor fuer Tumorgenetik, Universitaet zu Koeln, Josef-Stelzmann-Str. 9, D-50924, Koeln**Germany
JOURNAL: Journal of Immunotherapy 22 (6):p473-480 Nov., 1999
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recombinant receptors with antibody-like specificity for tumor-associated antigens were shown to direct specifically T cells to target tumor cells. Hodgkin and Reed-Sternberg cells, the malignant cell population in Hodgkin 's lymphoma, express high amounts of the cell surface antigen CD30. An anti-CD30 T-cell receptor with cellular activation properties is expected to graft T cells with specificity to Hodgkin cells. Here, the authors characterize a chimeric T-cell receptor with an extracellular domain consisting of the single-chain antibody fragment HRS3-scFv with specificity for the CD30 antigen and intracellular domain of the signal transducing part of the Fc-epsilon-I-gamma receptor. The HRS3-scFv was derived from the monoclonal anti-CD30 antibody HRS3 and retained specificity for the CD30 antigen. The recombinant HRS3-scFv-gamma receptor was expressed under control of the RSV-LTR after transfection into MD45 T-cells. The chimeric receptor protein is detected and analyzed by enzyme-l inked

immunosorbent assay (ELISA) and immunoprecipitation. Expression of the chimeric receptor converts MD45 T cells to specificity for CD30+ lymphoma cells. Specific cross-linking of the chimeric receptor with antigen resulted in cytolytic reactivity against CD30+ tumor cells in vitro. The results demonstrate that the chimeric receptor HRS3-scFv-gamma converts T cells to a specific MHC-unrestricted cytolytic response against CD30+ tumor cells offering an alternative strategy in cellular immunotherapy of Hodgkin 's disease.

15/7/27 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10338643 BIOSIS NO.: 199698793561
Anti-CD30 (BER-H2) immunotoxins containing the type-1 ribosome-inactivating proteins momordin and PAP-s (pokeweed antiviral protein from seeds) display powerful antitumor activity against CD30+ tumour cells in vitro and in SCID mice.
AUTHOR: Terenzi Adelmo; Bolognesi Andrea; Pasqualucci Laura; Flenghi Leonardo; Pileri Stefano; Stein Harald; Kadin Marshall; Bigerna Barbara; Polito Letizia; Tazzari Pier Luigi; Martelli Massimo F; Stirpe Fiorenzo; Falni Brunangelo(a)
AUTHOR ADDRESS: (a)Istituto Ematol., Policlinoco, Monteluce, 06100 Perugia **Italy
JOURNAL: British Journal of Haematology 92 (4):p872-879 1996
ISSN: 0007-1048
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The anti-CD30 immunotoxin (IT) Ber-H2/saporin is effective in patients with refractory Hodgkin 's disease. However, responses are short and partial, one of the main reasons being the inability to repeat IT doses because of formation of human antibodies against the murine antibody and/or the toxin. To overcome this problem, we constructed two new anti-CD30 ITs by covalently linking the mouse monoclonal antibody Ber-H2 to the type 1 ribosome-inactivating proteins (RIPs) momordin (MOM) and pokeweed antiviral protein from seeds (PAP-S), which do not cross-react with each other or with saporin. Both ITs inhibited protein synthesis by Hodgkin 's disease and anaplastic large-cell lymphoma (ALCL)-derived CD30+ target cell lines with a very high efficiency (IC-50 ranging from lt 5 times 10-13 M to 2.75 times 10-11 M, as RIP). In a SCID mouse model of xenografted CD30+ human ALCL, a 3 d treatment with non-toxic doses of Ber-H2/MOM (50% LD-50), started 24h after transplantation, prevented tumour development in about 40% of the animals and significantly delayed tumour growth rate in the others. Main toxicity signs in mice and rabbits were a dose-related increase of serum transaminases (AST and ALT) and creatine phosphokinase (CPK). LD-50 (as RIP) in Swiss mice was 7 mg/kg for Ber-H2/MOM and 0.45 mg/kg for Ber-H2/PAP-S. Sequential administration of two anti-CD30 ITs (Ber-H2/MOM and Ber-H2/saporin) was well tolerated and did not result in formation of antibodies cross-reacting with the two plant toxins. The results presented in this paper suggest that, in the future, sequential administration of anti-CD30 humanized antibodies linked to antigenically distinct type 1 RIPs (saporin, MOM, PAP-S) should be feasible.

15/7/28 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06927446 BIOSIS NO.: 000089060839
EVALUATION OF RICIN A CHAIN-CONTAINING IMMUNOTOXINS DIRECTED AGAINST THE CD30 ANTIGEN AS POTENTIAL REAGENTS FOR THE TREATMENT OF HODGKIN'S DISEASE
AUTHOR: ENGERT A; BURROWS F; JUNG W; TAZZARI P L; STEIN H; PFREUNDSCHUH M; DIEHL V; THORPE P
AUTHOR ADDRESS: DRUG TARGETING LAB., IMPERIAL CANCER RES. FUND, LONCOLN'S INN FIELDS, LONDON WC2A 3PX, UK.
JOURNAL: CANCER RES 50 (1). 1990. 84-88. 1990
FULL JOURNAL NAME: Cancer Research
CODEN: CNREA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Five monoclonal CD30 antibodies and two Fab' fragments were linked to deglycosylated ricin A chain (dgA), and their potential as immunotoxins for the treatment of Hodgkin 's disease was evaluated. Cross-blocking experiments demonstrated that HRS-1, HRS-3, HRS-4, and Ber-H2 recognize the same epitope on the CD30 antigen and that Ki-1 binds to a different epitope. Scatchard analyses showed that HRS-3, HRS-4, and Ber-H2 bound strongly to L540 Hodgkin cells (Kd 15, 7, and 14 mM, respectively), whereas HRS-1 and Ki-1 bound more weakly (Kd 160 and 380 mM, respectively). The different affinities of the antibodies correlated closely with their cytotoxic potency as immunotoxins. HRS-3.dgA, HRS-4.dgA, and Ber-H2.dgA inhibited the protein synthesis of L540 cells by 50% at concentrations of 0.9-2.0 .times. 10-10 M, whereas HRS-1.dgA and Ki-1.dgA were about 100 times less potent with 50% inhibitory concentrations of 0.8-1.0 .times. 10-8 M. The most effective immunotoxins, HRS-3.dgA and HRS-4.dgA, were only 15 times less toxic than ricin itself. HRS-3 Fab'.dgA and HRS-4 Fab'.dgA were 7.8 and 3 times less potent than their IgG.dgA counterparts with 50% inhibitory concentrations of 7 .times. 10-10 and 3 .times. 10-10 M, respectively. Staining of human tissues revealed an unexpected cross-reactivity of HRS-4 with pancreatic cells of malignant and nonmalignant origin. HRS-1, HRS-3, Ber-H2, and Ki-1 showed very little cross-reactivity with any normal human tissues. It is concluded that HRS-3.dgA and HRS-3 Fab'.dgA are the immunotoxins of choice for in vivo therapy .

15/7/29 (Item 1 from file: 315)
DIALOG(R)File 315:ChemEng & Biotec Abs

292769 CEABA Accession No.: 23-04-007163 DOCUMENT TYPE: Patent
Title: Improved CD- 30 antibodies and fragments thereof.
AUTHOR: Pfreundschuh, M.; Parker, D. L.
CODEN: PIXXD2
PATENT NUMBER: WO 9107437
PUBLICATION DATE: 30 May 1991 (910530) LANGUAGE: English
PRIORITY PATENT APPLICATION(S) & DATE(S): US 440051 (891120)
ABSTRACT: Novel toxin-conjugates can be administered to patients with

Hodgkin 's disease to specifically eliminate disease cells without being significantly toxic to non-disease cells.

15/7/30 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

11068193 EMBASE No: 2001075278
Bispecific antibody-mediated destruction of Hodgkin's lymphoma cells
Sundarapandiyan K.; Keler T.; Behnke D.; Engert A.; Barth S.; Matthey B.; Deo Y.M.; Graziano R.F.
R.F. Graziano, Medarex Inc., 1545 Route 22 East, Annandale, NJ 08801 United States
AUTHOR EMAIL: rgrazian@infi.net
Journal of Immunological Methods (J. IMMUNOL. METHODS) (Netherlands) 01 FEB 2001, 248/1-2 (113-123)
CODEN: JIMMB ISSN: 0022-1759
PUBLISHER ITEM IDENTIFIER: S0022175900003471
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

CD30 is a molecule that is overexpressed on the surface of Hodgkin 's lymphoma cells. Therefore, CD30 represents a potential candidate for immunotherapy. In this study, we report the in vitro results of two bispecific molecules (BSMs) that target CD30 to trigger molecules expressed on myeloid effector cells. The first BSM is composed of the Fabprime fragment of a CD30 -specific antibody , Ki-4, chemically linked to the Fabprime fragment of the humanized CD64 (FcgammaRI)-specific antibody, H22 (H22xKi-4). In the second BSM, the H22 Fabprime is replaced with the Fabprime fragment of the CD89 (FcalphaR)-specific, antibody, A77 (A77xKi-4). Both BSMs were able to bind specifically to lymphoma cell lines expressing CD30. In addition, the H22xKi-4 and A77xKi-4 BSMs were shown to bind cells expressing CD64 and CD89, respectively. Both BSMs mediated potent, dose-dependent antibody dependent cell-mediated cytotoxicity (ADCC) of CD30-expressing tumor cell lines when human monocytes were used as effector cells. In addition, freshly prepared polymorphonuclear leukocytes (PMNs) and effector cells in whole blood were able to mediate the ADCC of targets in conjunction with the A77xKi-4 BSM in some, but not all, experiments. Furthermore, we examined the ability of monocyte-derived macrophages (MDMs) to phagocytose CD30-expressing tumor cell lines in conjunction with the BSM. MDM-mediated phagocytosis was significantly enhanced in the presence of both BSMs. These results demonstrate that targeting lymphoma cells via CD30 to the myeloid high affinity Fc receptor for IgG and to the Fc receptor for IgA results in potent in vitro anti-tumor activity. (c) 2001 Elsevier Science B.V.

15/7/31 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06666567 EMBASE No: 1996331448
Future treatment strategies: Fact or fiction?
Schnell R.; Barth S.; Diehl V.; Engert A.
Department I of Internal Medicine, University of Cologne,

Josef-Stelzmann-Strasse 9,D-50924 Cologne Germany
Bailliere's Clinical Haematology (BAILLIERE'S CLIN. HAEMATOL.) (United Kingdom) 1996, 9/3 (573-593)
CODEN: BCHAE ISSN: 0950-3536
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Many new approaches involving biological agents have given promising results in experimental HD models. Clinical trials with immunotoxins, IL-2, Bi-Moabs or radioimmunoconjugates have demonstrated some clinical efficacy in patients with advanced refractory HD. Although it looks very unlikely to cure patients with larger tumour masses by either of these approaches, it might be feasible to treat bulky disease by conventional therapy first and then administer biological drugs to kill residual H-RS cells. Future phase-III trials will have to prove a possible superior effect of this combined immuno-/chemotherapy. In the meantime, the search for the most promising approach continues.

15/7/32 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06452005 EMBASE No: 1996104986
Anti-CD30 (BER-H2) immunotoxins containing the type-1 ribosome-inactivating proteins momordin and PAP-S (pokeweed antiviral protein from seeds) display powerful antitumour activity against CD30sup + tumour cells in vitro and in SCID mice

Terenzi A.; Bolognesi A.; Pasqualucci L.; Flenghi L.; Pileri S.; Stein H.; Kadin M.; Bigerna B.; Polito L.; Tazzari P.L.; Martelli M.F.; Stirpe F.; Falini B.
Istituto di Ematologia, Policlinico,06100 Perugia Italy
British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom) 1996, 92/4 (872-879)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The anti-CD30 immunotoxin (IT) Ber-H2/saporin is effective in patients with refractory Hodgkin 's disease. However, responses are short and partial, one of the main reasons being the inability to repeat IT doses because of formation of human antibodies against the murine antibody and/or the toxin. To overcome this problem, we constructed two new anti-CD30 ITs by covalently linking the mouse monoclonal antibody Ber-H2 to the type 1 ribosome-inactivating proteins (RIPs) momordin (MOM) and pokeweed antiviral protein from seeds (PAP-S), which do not cross-react with each other or with saporin. Both ITs inhibited protein synthesis by Hodgkin 's disease and anaplastic large-cell lymphoma (ALCL)-derived CD30sup + target cell lines with a very high efficiency (IC$D5inf 0 ranging from < 5 x 10sup -sup 1sup 3 M to 2.75 x 10sup -sup 1sup 1 M, as RIP). In a SCID mouse model of xenografted CD30sup + human ALCL, a 3 d treatment with non-toxic doses of Ber-H2/MOM (50% LD$D5inf 0), started 24 h after transplantation, prevented tumour development in about 40% of the animals and significantly delayed tumour growth rate in the others. Main toxicity signs in mice and rabbits were a dose-related increase of serum transaminases (AST and ALT) and creatine phosphokinase (CPK). LD$D5inf 0 (as RIP) in Swiss mice was 7 mg/kg for Ber-H2/MOM and 0.45 mg/kg for Ber-H2/PAP-S. Sequential administration

of two anti-CD30 ITs (Ber-H2/MOM and BER-H2/saporin) was well tolerated and did not result in formation of antibodies cross-reacting with the two plant toxins. The results presented in this paper suggest that, in the future, sequential administration of anti-CD30 humanized antibodies linked to antigenically distinct type 1 RIPs (saporin, MOM, PAP-S) should be feasible.

15/7/33 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

120239253 CA: 120(19)239253t PATENT
Antibody/radioisotope conjugate for tumor diagnosis and/or therapy
INVENTOR(AUTHOR): Stein, Harald; Falini, Brunangelo
LOCATION: Germany,
ASSIGNEE: Medac Gesellschaft fur Klinische Spezialpraeparate m.b.H.
PATENT: PCT International ; WO 9404189 A1 DATE: 940303
APPLICATION: WO 93EP2293 (930825) *EP 92250225 (920825)
PAGES: 44 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-043/00A; A61K-049/02B DESIGNATED COUNTRIES: AU; CA; FI; HU; JP; KR; NO; PL; RU; US
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA208009 Radiation Biochemistry
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals
IDENTIFIERS: antibody radioisotope conjugate tumor diagnosis, monoclonal antibody CD30 radioisotope conjugate, Hodgkin disease antibody radioisotope conjugate
DESCRIPTORS:
Hodgkin's disease... Neoplasm...
diagnosis of, monoclonal anti-CD30 antibody-radioisotope conjugates for
Neoplasm inhibitors...
monoclonal anti-CD30 antibody-radioisotope conjugates as
Antigens,CD30...
monoclonal antibody to, radioisotope conjugates of, for diagnosis and therapy of malignancy
Antibodies,monoclonal...
to CD30 antigen, radioisotope conjugates of, for diagnosis and therapy of malignancy
Radioelements,conjugates,compounds...
with monoclonal anti-CD30 antibody, for diagnosis of malignancy
Antibodies,conjugates...
with radioisotopes, for diagnosis and therapy of malignancy
CAS REGISTRY NUMBERS:
10043-66-0D anti-CD30 antigen antibody conjugates, uses, malignancy diagnosis and therapy with
7440-15-5D 7440-26-8D 7440-65-5D 7440-74-6D 7553-56-2D radioisotopes, anti-CD30 antigen antibody conjugates, uses, malignancy diagnosis and therapy with

15/7/34 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

119188616 CA: 119(18)188616h PATENT
Immunotoxins containing antibodies to CD30 antigen-positive cells for treatment of tumors
INVENTOR(AUTHOR): Falini, Brunangelo; Stirpe, Firenzo; Stein, Harald
LOCATION: Germany,
ASSIGNEE: Medac Gesellschaft fuer Klinische Spezialpraeparate mbH
PATENT: Germany Offen. ; DE 4205938 A1 DATE: 930902
APPLICATION: DE 4205938 (920227)
PAGES: 10 pp. CODEN: GWXXBX LANGUAGE: German CLASS: C07K-015/28A; A61K-039/395B
SECTION:
CA263006 Pharmaceuticals
CA215XXX Immunochemistry
IDENTIFIERS: immunotoxin CD30 antigen tumor treatment, antibody CD30 toxin conjugate tumor, ribosome inactivating protein antibody conjugate
DESCRIPTORS:
Glycoproteins,specific or class...
bryodin, conjugates with monoclonal antibody to CD30 antigen, for tumor treatment
Proteins,specific or class, RIP (ribosome-inactivating protein), type 1...
conjugates, with monoclonal antibody to CD30 antigen, for tumor treatment
Glycoproteins,specific or class...
dinathin, conjugates with monoclonal antibody to CD30 antigen, for tumor treatment
Linking agents...
heterobifunctional, monoclonal antibody to CD30 antigen conjugation with type 1 ribosome-inactivating protein with, for tumor treatment
Neoplasm inhibitors... Neoplasm inhibitors,Hodgkin's disease...
immunotoxin contg. monoclonal antibody to CD30 antigen and plant type 1 ribosome-inactivating protein
Glycoproteins,specific or class...
momorcochin-S, conjugates with monoclonal antibody to CD30 antigen, for tumor treatment
Pharmaceutical dosage forms,immunotoxins...
monoclonal antibody to CD30 antigen and plant type 1 ribosome-inactivating protein in, for tumor treatment
Antigens,CD30...
monoclonal antibody to, conjugates with plant type 1 ribosome-inactivating proteins, for tumor treatment
Antibodies,monoclonal...
to CD30 antigen, conjugates with plant type 1 ribosome-inactivating proteins, for tumor treatment
Proteins,specific or class, momordins, conjugates... Proteins,specific or class, PAP (pokeweed antiviral protein), conjugates... Proteins,specific or class, saporins 6, conjugates... Proteins,specific or class, saporins, conjugates... Proteins,specific or class, trichosanthins, conjugates...
with monoclonal antibody to CD30 antigen, for tumor treatment
CAS REGISTRY NUMBERS:
75037-46-6D conjugates with monoclonal antibody to CD30 antigen, for tumor treatment
111-30-8 151-51-9 6539-14-6 6953-60-2 68181-17-9 monoclonal antibody to CD30 antigen conjugation with type 1 ribosome-inactivating protein with, for tumor treatment

15/7/35 (Item 3 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

117142942 CA: 117(15)142942s JOURNAL
Ber-H2 (anti-CD30)-saporin immunotoxin: a new tool for the treatment of Hodgkin's disease and CD30 + lymphoma: in vitro evaluation
AUTHOR(S): Tazzari, Pier Luigi; Bolognesi, Andrea; De Totero, Daniela; Falini, Brunangelo; Lemoli, Roberto M.; Soria, Marco R.; Pileri, Stefano; Gobbi, Marco; Stein, Harald; et al.
LOCATION: Ist. Naz. Ric. Cancro, Genoa, Italy
JOURNAL: Br. J. Haematol. DATE: 1992 VOLUME: 81 NUMBER: 2 PAGES: 203-11 CODEN: BJHEAL ISSN: 0007-1048 LANGUAGE: English
SECTION:
CA201006 Pharmacology
CA263XXX Pharmaceuticals
IDENTIFIERS: immunotoxin monoclonal antibody saporin conjugate lymphoma, Hodgkin lymphoma immunotoxin
DESCRIPTORS:
Antibodies,monoclonal, conjugates...
Ber-H2 (anti-CD30), with saporin, for treatment of Hodgkin's lymphoma
Pharmaceutical dosage forms,immunotoxins...
Ber-H2 (anti-CD30)-saporin conjugate as, for treatment of Hodgkin's lymphoma
Neoplasm inhibitors...
Ber-H2 (anti-CD30)-saporin immunotoxin as, in Hodgkin's disease
Hodgkin's disease...
Ber-H2 (anti-CD30)-saporin immunotoxin as inhibitors of
Proteins,specific or class, saporins, conjugates...
with anti-CD30 monoclonal antibody, for treatment of Hodgkin's lymphoma

15/7/36 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

013699776
WPI Acc No: 2001-184000/200119
New Fv-antibody construct, useful for treating Hodgkin and Reed-Sternberg diseases, has binding sites for CD16 receptor and CD30 surface protein
Patent Assignee: DEUT KREBSFORSCHUNGSZENTRUM (DEKR-N)
Inventor: ARNDT M; KIPRIYANOV S; KRAUSS J; LITTLE M; PFREUNDSCHUH M; KYPRIYANOV S
Number of Countries: 094 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 19937264	A1	20010215	DE 1037264	A	19990806	200119	B
WO 200111059	A1	20010215	WO 2000DE2589	A	20000802	200119	
AU 200069825	A	20010305	AU 200069825	A	20000802	200130	

Priority Applications (No Type Date): DE 1037264 A 19990806
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
DE 19937264	A1		18	C07K-016/00	
WO 200111059	A1	G		C12N-015/70	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE

KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
AU 200069825 A C12N-015/70 Based on patent WO 200111059

Abstract (Basic): DE 19937264 A1

NOVELTY - An Fv-antibody construct (I) having binding sites for a CD16 receptor and a CD30 surface protein, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) expression vector encoding (I);

(2) transformants containing the vector of (1);

(3) preparation of (I) by culturing cells of (2); and

(4) kit comprising (I) and/or the vector of (1), and auxiliaries such as buffers, solvents, carriers, controls and labels, or their replacements.

ACTIVITY - Cytostatic.

CD30+ L540CY Hodgkin disease cells (15 million) were implanted subcutaneously into the flank of mice and when the tumors had grown to diameter 4-6 mm, the animals were treated by intravenous injection of 0.1 mg (I) plus peripheral blood lymphocytes (PBL, including natural killer cells). The volume of treated tumors declined to zero within 7 days, but tumors continued to grow in animals treated with either (I) or the PBL alone, or with a mixture of separate anti-CD16 and anti-CD30 antibodies .

MECHANISM OF ACTION - (I) causes lysis of CD30+, specifically tumor, cells. It activates natural killer cells, through the CD16 receptor, and directs them to CD30-expressing cells.

USE - (I) are used to treat diseases in which CD30+ cells are implicated, particularly tumors and specifically Hodgkin or Reed-Sternberg diseases.

ADVANTAGE - (I) have a stronger lytic action than known bispecific antibodies, can be produced on a large scale with high purity, and contain no components that can induce unwanted immune responses.

pp; 18 DwgNo 0/4

Derwent Class: B04; D16
International Patent Class (Main): C07K-016/00; C12N-015/70
International Patent Class (Additional): A61K-039/395; A61P-035/00; C07K-019/00; C12N-001/21

15/7/37 (Item 2 from file: 351)
DIALOG(R)File 351:Derwent WPI

011010067
WPI Acc No: 1996-507017/199651
DNA mols. encoding CD30-specific immunoglobulin variable regions - useful for cancer diagnosis or therapy
Patent Assignee: MEDAC GES KLINISCHE SPEZIALPRAEPARATE (MEDA-N)
Inventor: STEIN H; ZIEGLER A
Number of Countries: 072 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 19543039	C1	19961121	DE 1043039	A	19951108	199651	B
WO 9717374	A1	19970515	WO 96EP4765	A	19961102	199725	

AU 9674971 A 19970529 AU 9674971 A 19961102 199737

Priority Applications (No Type Date): DE 1043039 A 19951108
Cited Patents: 2.Jnl.Ref; DE 4205938; EP 256654; WO 8909622; WO 9107437; WO 9109966; WO 9404189
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
DE 19543039	C1		20		
WO 9717374	A1	G	442		

Designated States (National): AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

AU 9674971 A Based on patent WO 9717374

Abstract (Basic): DE 19543039 C

Recombinant DNA mols. which encode immunoglobulin variable regions having specificity for the human cell-membrane antigen CD30 and which comprise one or more of four defined sequences (470, 598, 412 or 777 bp) given in the specification, or fragments of these sequences, are new. Also claimed are: (1) expression vectors contg. one or more of the above recombinant DNA mols. linked to expression control sequences; (2) host cells transformed with the vectors of (1); and (3) recombinant CD30 ligands comprising one or both of a 141 and a 136 amino acid sequence (given in the specification), or fragments of these sequences.

USE - The ligands are useful for diagnosis or therapy of CD30-expressing cancers, esp. Hodgkinson 's disease.

Dwg.0/0

Derwent Class: B04; D16; J04; K08; S03
International Patent Class (Main): C07K-016/46; C12N-015/79
International Patent Class (Additional): A61K-039/395; C07K-016/18; C07K-016/28; C07K-016/30; C12N-001/00; C12N-001/21; C12N-005/10; C12N-015/11; C12N-015/70; C12N-015/74; G01N-033/53; G01N-033/574

15/7/38 (Item 3 from file: 351)
DIALOG(R)File 351:Derwent WPI

010857588
WPI Acc No: 1996-354541/199635
Anti- CD30 antibodies which prevent cleavage of membranes bound CD30 antigen - are used to prepare immuno-toxin conjugates specific for Hodgkin's disease cells
Patent Assignee: BOEHRINGER MANNHEIM GMBH (BOEF); ROCHE DIAGNOSTICS GMBH (HOFF)
Inventor: HANSEN H; LEMKE H
Number of Countries: 071 Number of Patents: 009
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9622384	A1	19960725	WO 96EP98	A	19960111	199635	B
AU 9644856	A	19960807	AU 9644856	A	19960111	199646	
EP 805871	A1	19971112	EP 96900937	A	19960111	199750	
			WO 96EP98	A	19960111		
JP 10502544	W	19980310	JP 96522015	A	19960111	199820	

EP 805871	B1	19991117	WO 96EP98	A	19960111	
			EP 96900937	A	19960111	199953
DE 69605181	E	19991223	WO 96EP98	A	19960111	
			DE 605181	A	19960111	200006
			EP 96900937	A	19960111	
US 6033876	A	20000307	WO 96EP98	A	19960111	
			WO 96EP98	A	19960111	200019
			US 97860727	A	19970926	
ES 2141467	T3	20000316	EP 96900937	A	19960111	200021
JP 3066983	B2	20000717	JP 96522015	A	19960111	200039
			WO 96EP98	A	19960111	

Priority Applications (No Type Date): EP 95100591 A 19950118
Cited Patents: 4.Jnl.Ref; DE 4205938; WO 9107437
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9622384	A1	E	30	C12P-021/08	

Designated States (National): AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
Designated States (Regional): AT BE CH DE DK EA ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

AU 9644856	A		C12P-021/08	Based on patent WO 9622384
EP 805871	A1	E	C12P-021/08	Based on patent WO 9622384

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

JP 10502544	W	42	C12N-015/02	Based on patent WO 9622384
EP 805871	B1	E	C12P-021/08	Based on patent WO 9622384

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

DE 69605181	E		C12P-021/08	Based on patent EP 805871
				Based on patent WO 9622384
US 6033876	A		A61K-039/395	Based on patent WO 9622384
ES 2141467	T3		C12P-021/08	Based on patent EP 805871
JP 3066983	B2	11	C12N-015/02	Previous Publ. patent JP 10502544
				Based on patent WO 9622384

Abstract (Basic): WO 9622384 A

An antibody (A) which binds to the CD30 antigen is new. (A) releases sCD30 from Hodgkin 's disease cells to an amt. of up to 10% of that released without addn. of the antibody. (A) does not bind to B cell non-Hodgkin 's lymphomas or plasma cells to any great extent. Also claimed are: (1) the cell line DSM ACC 2204; (2) a process for the prodn. of (A), where (i) a mammal is immunised with a Hodgkin 's disease cell line; (ii) anti-CD30 antibody producing B cells are isolated and fused with myeloma cell lines; (iii) the fused cell lines are isolated and tested for antibody activity against Hodgkin 's disease cells, and for the release of sCD30 from the cells; (iv) the cell lines which produce antibodies which bind to Hodgkin 's disease cell lines but not to B cell non-Hodgkin 's lymphomas or plasma cells and release up to 10% sCD30 are isolated, and (v) monoclonal antibodies are isolated from those cell lines, and (3) a pharmaceutical compsn. contg. (A).

A) is obtd. from the cell line DSM ACC 2204, and is a Fab, Fab', or F(ab')2 fragment. (A) may be linked to a toxin, and pref. is modified to give reduced immunogenicity in humans, linking the variable regions of Ki-4 to constant regions of a human antibody. The Ki-4

constant region is pref. further modified, having part or all the non-CD30 binding sequences replaced by the corresp. sequences from a human variable region. (A) is partic. a CDR-grafted antibody.

USE - (A) prevents proteolytic cleavage and release of membrane-bound CD30 antigen. It can be used to mfr. an antibody-toxin conjugate for use as a therapeutic agent for the treatment of Hodgkin 's disease.

ADVANTAGE - The antibodies exhibit an almost complete inhibitions of the formation of the sCD30, in direct contrast to previous antibodies which enhanced the release. The antibodies are specific for Hodgkin and Reed-Sternberg cells.

Dwg.0/0

Derwent Class: B04; D16
International Patent Class (Main): A61K-039/395; C12N-015/02
International Patent Class (Additional): C07K-016/30; C12N-005/20; C12N-015/06; C12N-015/13; C12P-021/08; G01N-033/53

15/7/39 (Item 4 from file: 351)
DIALOG(R)File 351:Derwent WPI

009988653
WPI Acc No: 1994-256364/199432
Prodn. of hybridoma cell lines producing anti-CD16 antibodies - by co-culturing hybridoma cells producing antibodies and unstimulated human NK cells, used for prodn. of bispecific antibodies for tumour therapy
Patent Assignee: BIOTEST PHARMA GMBH (BIOT)
Inventor: PFREUNDSCHUH M
Number of Countries: 009 Number of Patents: 004
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 4337197	C1	19940825	DE 4337197	A	19931030	199432	B
EP 657533	A1	19950614	EP 94116611	A	19941021	199528	
JP 7246091	A	19950926	JP 94265392	A	19941028	199547	
US 5643759	A	19970701	US 94327254	A	19941021	199732	

Priority Applications (No Type Date): DE 4337197 A 19931030
Cited Patents: 04Jnl.Ref; WO 9107437
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
DE 4337197	C1		14	C12N-005/12	
EP 657533	A1	G		C12N-015/06	
Designated States (Regional): AT CH DE FR GB IT LI					
JP 7246091	A		9	C12N-005/10	
US 5643759	A		13	C12P-021/08	

Abstract (Basic): DE 4337197 C

Selective prodn. of hybridoma cell lines which produce a murine monoclonal antibody which is of class IgG1, is directed against human CD16 antigen and has a high capacity for inducing NKC-dependent cytotoxicity (NKC=natural killer cell), comprises: (a) co-culturing hybridoma cells producing anti-CD16 monoclonal antibodies together with unstimulated human NK cells; (b) monitoring the mortality rate of the hybridoma cells; and (c) selecting the hybridoma cells with the highest mortality rate.

Also claimed is hybridoma cell line A9 (DSM ACC2148) which produces

a monoclonal antibody which is of subclass IgG1-lambda, is directed against human CD16 antigen, has a high capacity for inducing NKC-dependent cytotoxicity, and binds to a CD16 epitope separate from that recognised by monoclonal antibody 3G8.

Also claimed is a process for producing bispecific monoclonal antibodies, comprising fusing hybridoma cells produced as above with HRS-3 hybridoma cells (producing anti-CD30 antibody) to obtain a tetradoma, and isolating and purifying the resulting bispecific antibodies.

Step (a) is pref. effected in the presence of granulocytes. Step (b) comprises comparing the anti-CD16 activity with that of control hybridoma cells producing anti-CD16 antibodies. For prodn. of bispecific antibodies, A9 hybridoma cells are fused with the HRS-3 cells.

USE - The bispecific antibodies are useful for inducing NKC-mediated cytotoxicity against human tumour cells to cause regression of established tumours, esp. in Hodgkin 's disease.

Dwg.0/8

Abstract (Equivalent): US 5643759 A

A novel method for preparing bispecific MAB's, comprises fusing a hybridoma cell, A9, which produces a murine MAB of class IgG1 with a high capacity for inducing NK cell-related cytotoxicity, whereas the MAB is specific for human CD16 antigen, with hybridoma cells HRS-3 which binds human CD30 antigen to form a tetradoma HRS-3/A9 of deposit account number ACC 2142 thereby to obtain a bispecific MAB and isolating bispecific MAB, the hybridoma cell line A9 having been produced by

a. co-culturing hybridoma cell line A9 of deposit number ACC 2148 which produces CD 16 MAB with unstimulated human NK cells,

b. determining the die-off rate of the hybridoma cells and then

c. selecting the hybridoma cells with the highest die-off rate.

Dwg.0/8

Derwent Class: B04; D16

International Patent Class (Main): C12N-005/10; C12N-005/12; C12N-015/06; C12P-021/08

International Patent Class (Additional): A61K-039/395; C07K-015/28; C07K-016/00; C07K-016/18; C07K-016/28; C07K-016/30; C12N-005/20; C12N-015/02; C12P-021/08; C12R-001-91

15/7/40 (Item 5 from file: 351)

DIALOG(R)File 351:Derwent WPI

009802988

WPI Acc No: 1994-082842/199410

Compsn. contg. radiolabelled antibody specific for CD30 surface antigen - for radioimaging detection and treatment of CD30 positive tumours, partic. Hodgkin's disease

Patent Assignee: MEDAC GES KLINISCHE SPEZIALPRAEPARATE (MEDA-N)

Inventor: FALINI B; STEIN H

Number of Countries: 026 Number of Patents: 002

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9404189	A1	19940303	WO 93EP2293	A	19930825	199410	B
AU 9349536	A	19940315	AU 9349536	A	19930825	199428	

Priority Applications (No Type Date): EP 92250225 A 19920825
Cited Patents: 6.Jnl.Ref; WO 9107437; WO 9317715
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 9404189 A1 43 A61K-043/00
Designated States (National): AU CA FI HU JP KR NO PL RU US
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
AU 9349536 A A61K-043/00 Based on patent WO 9404189

Abstract (Basic): WO 9404189 A

Therapeutic and diagnostic compsn. contains an antibody conjugate (A) consisting of (1) monoclonal antibody (MAb) which binds to the CD30 cell surface antigen and (2) a radioactive isotope linked to MAb directly, through a linker or via a chelating agent. Pref. MAb is the murine antibody Ber-H2, or an antibody that recognises the Ber-H2 epitope, and the isotope is of I, Y, In, Tc or Re.

USE/ADVANTAGE - The compsn. is used (a) to detect tumour cells by radioimaging and (b) to treat human malignancies which express CD30, esp. Hodgkin 's disease and anaplastic large cell lymphoma (ALC), partic. cases resistant to conventional therapy . MAb have high binding affinity and specificity, with little if any crossreactivity with other tissues (and thus reduced side effects). Only low doses of (A) are required; MAb reach tumour cells after intravenous injection; saturate binding sites and persist on the tumour cells for at least 72 hr.

Dwg.0/6

Derwent Class: B04; D16; K08
International Patent Class (Main): A61K-043/00
International Patent Class (Additional): A61K-049/02

15/7/41 (Item 6 from file: 351)
DIALOG(R)File 351:Derwent WPI

009587886
WPI Acc No: 1993-281432/199336
New immuno-toxin contg. CD30 monoclonal antibody - is coupled to type 1 ribosome inactivating protein toxin, for selective elimination of CD30 cells, esp. treatment of Hodgkins disease
Patent Assignee: MEDAC GES KLINISCHE SPEZIALPRAEPARATE (MEDA-N)
Inventor: FALINI B; STEIN H; STIRPE F
Number of Countries: 001 Number of Patents: 001
Patent Family:
Patent No Kind Date Applicat No Kind Date Week
DE 4205938 A1 19930902 DE 4205938 A 19920227 199336 B

Priority Applications (No Type Date): DE 4205938 A 19920227
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
DE 4205938 A1 10 C07K-015/28

Abstract (Basic): DE 4205938 A

New immunotoxin (I) comprises monoclonal CD30 antibodies (Ab) covalently bonded to a ribosome-inactivating protein type-1 toxin (II). Pref. Ab is of the Ber-H2 type while (II) is bryodin; the toxin

purified from Asparagus officinalis; momorcochin-5; dianthin; gelonin; trichosanthin or pref. saporin; PAP (from Phytolacca americana seeds) and/or momordin.

Ab, esp. Ber-H2 from the hybridoma ECACC 92012823, and (II) are coupled using a heterobifunctional reagent, e.g. N-succininidyl-3-(2-pyridyldithio)propionate; S-acetyl-mercaptosuccinic anhydride; a carbodiimide; glutaraldehyde or esp. 2-iminothiolan (2-IT; sec Br. J cancer, 60 (1989) 315). Ab is isolated from hybridoma culture supernatant (or ascites) by affinity chromatography on protein A and then hydroxyapatite chromatography. It is derivatised with 2-IT in pH9 borate buffer then incubated for 20 hr at room temp. with 2-IT-derivatised toxin (reduced with dithiothreitol). The reaction mixt. was gel. filtered on 'Sephacryl S-200' (RTM) and the fractions contg. the low molecular wt. conjugate isolated (esp. it has mole ratio (II): Ab = 1-3).

USE/ADVANTAGE - (I) can be used (1) for treating tumours and (2) for selective elimination, in vivo or ex vivo, of CD-30 positive cells. They are more active than similar immuno toxins prepd. from ricin A chain and give partic. good results in cases of Hodgkin 's disease. (I) is administered by intramuscular or intravenous injection (as a soln. or suspension) to provide a dose of 0.01-5 (pref. 0.01-0.5) mg/kg, given one or more times per day for one to several weeks.

Dwg.0/2

Derwent Class: B04; D16

International Patent Class (Main): C07K-015/28

International Patent Class (Additional): A61K-039/395

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